# Guidance for Industry

# Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act

## *DRAFT GUIDANCE*

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**July 2009**
**Drug Safety**

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**U.S. Department of Health and Human Services**
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# TABLE OF CONTENTS

# Guidance for Industry[1]

# Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION

This guidance provides information on the implementation of new section 505(o) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(o)), added by section 901 of the Food, and Drug Administration Amendments Act of 2007 (FDAAA). Section 505(o) authorizes FDA to require certain postmarketing studies and clinical trials[2] for prescription drug and biological products approved under section 505 of the Act or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). This guidance provides information about the requirements for postmarketing studies and clinical trials under section 505(o) of the Act. The guidance also describes the types of postmarketing studies and clinical trials that:

- will generally be required under the new legislation (postmarketing requirements (PMRs)) and
- will generally be agreed-upon commitments (postmarketing commitments (PMCs)) because they do not meet the new statutory criteria for required postmarketing studies and clinical trials.

[1] This guidance has been prepared by the FDAAA Title IX Working Group comprising staff from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] FDAAA makes a new distinction between "study" and "clinical trial." Previous laws, regulations, and practice have used the terms *studies* and *trials* interchangeably. For example, section 506B of the Act (21 U.S.C. 356b) uses "studies" to describe the postmarketing commitments (PMCs) that must be reported annually, including clinical trials. For purposes of implementing section 505(o)(3) of the Act, because FDAAA distinguishes between studies and clinical trials and section 505(o) provides criteria to determine which may be required (see section II.B of this guidance), we distinguish between studies and clinical trials for the purposes described in this document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

This guidance does not apply to nonprescription drugs approved under a new drug application (NDA) or generic drugs approved under section 505(j) of the Act because section 505(o) of the Act applies only to prescription drug and biological products approved under section 505(b) of the Act or section 351 of the PHS Act.

## II. BACKGROUND

On September 27, 2007, the President signed FDAAA (Public Law 110-85). Section 901 of Title IX of FDAAA amended the Act by adding new section 505(o). Section 505(o) authorizes FDA to require certain postmarketing studies and clinical trials for prescription drug and biological products approved under section 505 of the Act or section 351 of the PHS Act.

### A. Past Practice

In the past, FDA has used the term *postmarketing commitment (PMC)* to refer to studies (including clinical trials), conducted by an applicant after FDA has approved a drug for marketing or licensing, that were intended to further refine the safety, efficacy, or optimal use of a product or to ensure consistency and reliability of product quality. These PMCs were either agreed upon by FDA and the applicant or, under certain circumstances, required by FDA. Prior to the passage of FDAAA, FDA required PMCs in the following situations:

- Subpart H and subpart E accelerated approvals for products approved under 505(b) of the Act or section 351 of the PHS Act, respectively**,** which require postmarketing studies to demonstrate clinical benefit (21 CFR 314.510 and 601.41);
- Deferred pediatric studies, where studies are required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)); and
- Animal Efficacy Rule approvals, where studies to demonstrate safety and efficacy in humans are required at the time of use (21 CFR 314.610(b)(1) and 601.91(b)(1)).

Section 130(a) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) amended the Act by adding a new provision requiring reports of certain postmarketing studies for human drug and biological products (section 506B of the Act (21 U.S.C. 356b)). Section 506B of the Act provides FDA with additional authority to monitor the progress of a PMC by requiring the applicant to submit a report annually providing information on the status of the PMC, which was defined to include agreed-upon commitments and required

studies (including clinical trials).[3] This report must also include the reasons, if any, for failure to complete the commitment. This provision is implemented at 21 CFR 314.81(b)(2)(vii) and 601.70.[4] Under section 506B(b) and (c), FDA is required to track these PMCs and report on them annually in the *Federal Register*.[5]

## B. New FDAAA Authority and Requirements

### *1. FDA May Require Applicants to Conduct Studies and Clinical Trials*

Section 505(o) of the Act authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of *new safety information*.[6] Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicate the potential for a serious risk

For the purposes of implementing section 901 of FDAAA,[7] clinical trials and studies are defined as follows:

- ***Clinical trials*** are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects.

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[3] See the guidance for industry, *Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (guidance on the status of PMCs), available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] In addition, new drug application (NDA) applicants are required by 21 CFR 314.81(b)(2)(viii) to report annually to FDA on postmarketing studies or trials that are not 506B studies or trials. Such studies or trials are not required, and they include chemistry, manufacturing, and controls (CMC) studies that applicants have agreed with FDA to conduct (CMC commitments), and all product stability studies that applicants have agreed with FDA to conduct (stability studies). The reporting requirement at 21 CFR 314.81(b)(2)(viii) also includes "any postmarketing study not included under [§314.81](b)(2)(vii) . . . that is being performed by, or on behalf of, the applicant." Reports on the status of these types of studies are not reports required under section 506B.

[5] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

[6] Defined at section 505-1(b)(3) of the Act (see Glossary).

[7] These definitions of postmarketing clinical trial and study do not affect whether the trials or studies are subject to the requirements of Title VIII of FDAAA (Clinical Trial Databases) and section 402(j) of the PHS Act (42 U.S.C. 282(j)).

- ***Studies*** are all other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

FDA has separately defined these terms because statutory provisions in section 505(o) of the Act differentiate between studies and clinical trials:

- Under section 505(o)(3)(D)(i), before requiring a ***postmarketing study***, FDA must find that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) of the Act will not be sufficient to meet the purposes described in section 505(o)(3)(B).
- Under section 505(o)(3)(D)(ii), before requiring a ***postmarketing clinical trial***, FDA must find that a postmarketing study will not be sufficient to meet the purposes described in section 505(o)(3)(B).

*2. Applicants Are Required to Report on the Status of Studies and Clinical Trials*

The applicant is required to provide certain information to FDA with regard to required postmarketing studies and clinical trials (section 505(o)(3)(E)(ii)). Under section 505(o)(3)(E)(ii), this information must include:

- For all required postmarketing studies and clinical trials, a timetable for completion
- For each study required under section 505(o), periodic reports on the status of the study, including whether any difficulties in completing the study have been encountered
- For each clinical trial required under section 505(o), periodic reports on the status of the clinical trial, including:
  - whether enrollment has begun,
  - the number of participants enrolled,
  - the expected completion date,
  - whether any difficulties completing the clinical trial have been encountered, and
  - registration information with respect to the clinical trial under section 402(j) of the PHS Act (42 U.S.C. 282(j))

In addition, FDAAA requires that applicants report on each study and clinical trial "otherwise undertaken by the applicant to investigate a safety issue" (see section 505(o)(3)(E)(ii)). Reports on these studies and clinical trials would have previously been required under 21 CFR 314.81(b)(2)(viii).

## III. IMPLEMENTATION OF POSTMARKETING STUDY AND CLINICAL TRIAL REQUIREMENTS UNDER FDAAA[8]

Under section 505(o)(3) of the Act, FDA will require applicants to conduct a postmarketing study or studies or clinical trial(s) when the following conditions are met:

1. When the decision to require a postmarketing study or clinical trial is based on scientific data deemed appropriate by FDA, including information regarding chemically-related or pharmacologically-related drugs; and

2. When FDA has found —
   a. before requiring a postmarketing study, that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) will not be sufficient to meet the purposes described in condition 3 below; and
   b. before requiring a postmarketing clinical trial, that a postmarketing study will not be sufficient to meet the purposes in condition 3 below; and

3. When the purposes of the study or clinical trial, as described in section 505(o)(3)(B), are one or more of the following:
   - To assess a known serious risk related to the use of the drug
   - To assess signals of serious risk related to the use of the drug
   - To identify an unexpected serious risk when available data indicates the potential for a serious risk

When these conditions are met, the Agency intends to require the study or clinical trial as a *postmarketing requirement (PMR)*.

The purposes outlined in section 505(o)(3)(B) are all related to drug safety. Although almost any study or clinical trial might be broadly construed to evaluate safety, FDA does not intend to consider all postmarketing studies and clinical trials as PMRs.

- The term ***postmarketing requirement*** or ***PMR*** will be used to describe **all** required postmarketing studies or clinical trials, including those required under FDAAA and those required under subpart H of 21 CFR part 314, subpart E of 21 CFR part 601, the Pediatric Research Equity Act, and the Animal Efficacy Rule (formerly called PMCs).
- The term ***postmarketing commitment*** or ***PMC*** will be used to describe studies and clinical trials that applicants have agreed to conduct, but that will generally not be considered as meeting the statutory purposes and so will not be required.

FDA is providing guidance on categories of postmarketing studies and clinical trials that will generally be considered as meeting the conditions described above and will be PMRs (section

[8] Applicants conducting postmarketing studies and clinical trials must continue to comply with 21 CFR part 312 and 21 CFR part 58 when applicable, and Health and Human Services (HHS) and FDA human subject protection regulations at 45 CFR part 46 and 21 CFR parts 50 and 56 when applicable.

III.A). We are also providing guidance on categories of studies and clinical trials that will generally not be required by statute or regulation, but may be PMCs (section III.B)

### A. Postmarketing Requirements (PMRs)

PMRs under FDAAA generally would include, but not be limited to, the following:

- Observational pharmacoepidemiologic studies designed to assess a serious risk attributed to a drug exposure or to quantify risk or evaluate factors that affect the risk of serious toxicity, such as drug dose, timing of exposure, or patient characteristics. To facilitate interpretation of the findings, the studies should have a protocol and control group, unless there is a scientifically valid reason to exclude controls, and test prespecified hypotheses. Data sources for these studies could include administrative healthcare claims data, electronic medical records, registries[9], prospectively collected observational data, or other sources of observational data. Examples include studies designed to:

  - Estimate the relative risk of a serious adverse event or toxicity associated with use of a drug
  - Provide estimates of risk (e.g., incidence rates) for a serious adverse event or toxicity
  - Obtain long-term clinical outcome data, including information about potentially rare serious adverse events in patients taking the drug compared to patients not exposed to the drug
  - Compare pregnancy incidence and fetal/child outcomes after patient drug exposure compared to patients who did not receive the drug

- Clinical trials with a primary safety endpoint, evaluated with prespecified assessments. While efficacy may be evaluated, the primary goal of the PMR would be to evaluate safety. Examples include clinical trials designed to:

  - Evaluate the occurrence of asthma exacerbations associated with the use of inhalation treatments for asthma in a controlled clinical trial
  - Determine the incidence of myocardial ischemia or infarction, malignancy, and mortality in patients treated with the approved drug on a chronic basis
  - Evaluate differences in safety between patients withdrawn from treatment after some period of treatment and patients who remain on the treatment
  - Evaluate the potential for Q-T prolongation in a thorough Q-T clinical trial
  - Determine growth and neurocognitive function in pediatric patients treated chronically with the drug

[9] Registries that are established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required under a REMS. Registries may also serve as a repository for clinical data and allow for case finding and follow-up. These registries are not considered PMRs, but studies conducted using the data may be.

  - Evaluate safety in a particular racial or ethnic group or vulnerable population such as the immunocompromised
  - Evaluate the safety of the drug in pregnant women
  - Evaluate drug toxicity in patients with hepatic or renal impairment
  - Evaluate long-term safety of cell and gene therapy products depending on the type of vector used and the inherent risk of integration
  - Evaluate the safety of a drug in patients with HIV-1 co-infected with hepatitis C or B

- Safety studies in animals investigating specific end-organ toxicities, including, but not limited to, carcinogenicity and reproductive toxicity studies. Examples include studies designed to:

  - Assess carcinogenic potential in appropriate species (i.e., mice and rats)
  - Assess the potential for reproductive toxicology in appropriate species (i.e., monkeys or rabbits)

- In vitro laboratory safety studies designed to, for example:

  - Assess certain receptor affinities for any circulating or major metabolites, including conjugates, to evaluate the potential for off-target binding and resulting serious risk
  - Determine if resistance to a drug has developed in those organisms specific to the labeled indication, resulting in increased serious risk
  - Define the mechanism of drug resistance for certain organisms
  - Assess the risk of cross-contamination between products that could result from sharing product-contacting equipment and parts
  - Validate the accuracy, precision, sensitivity, specificity, and robustness of an immunogenicity assay for a drug or biological product to assess an immunologic safety concern

- Studies or clinical trials to evaluate the pharmacokinetics of the drug in the labeled population or in a subpopulation at potential risk for high drug exposures that could lead to toxicity. Examples include studies or clinical trials designed to:

  - Determine the optimal dose for maintenance therapy in patients with chronic renal disease, a population at risk for drug accumulation
  - Study the pharmacokinetic profile in a rodent model of hepatic dysfunction in order to evaluate the potential for toxicity in patients with liver impairment

- Studies or clinical trials designed to evaluate drug interactions or bioavailability when there are scientific data that indicate the potential for a serious safety risk. Examples include studies or clinical trials to:

  - Assess in vitro p-glycoprotein substrates

- — Assess potential interactions of an approved drug with a frequently concomitantly prescribed medication
- — Evaluate whether multiple doses of an approved drug alter the metabolism of a sensitive CYP2C9 substrate
- — Evaluate bioavailability of an oral drug in the presence of food

### B. Postmarketing Commitments (PMCs)

Generally, the following types of studies or clinical trials would not meet the statutory purposes for PMRs, but might be considered for agreed-upon PMCs:

- Drug and biologic quality studies, including manufacturing, stability, and immunogenicity studies, that do not have a safety endpoint, such as studies designed to:
  - — Develop an optical rotation test, collect data on commercial batches, and use the data to update drug substance specification standards
  - — Evaluate immune response to concomitant vaccination(s) that are a part of routine U.S. immunization practice
- Pharmacoepidemiologic studies designed to examine the natural history of a disease or to estimate background rates for adverse events.[10]
- Clinical trials in which the primary endpoint is related to further defining efficacy, designed to:
  - — Evaluate efficacy using a withdrawal design
  - — Evaluate long-term effectiveness or duration of response

## IV. PROCEDURES

As outlined in section X.B of the PDUFA Reauthorization Performance Goals and Procedures, FY 2008-2012,[11] FDA plans to inform the applicant of the planned target date for communication of feedback from the review division to the applicant regarding PMRs and PMCs. FDA plans to communicate the planned target date in a letter sent within 14 days of the 60-day filing date.

FDA plans to send a list of potential PMRs and PMCs, clearly delineated as to be required and to be agreed upon, to the applicant near the target date. The applicant will have the opportunity to

[10] Postmarketing commitments can include surveillance and observational studies conducted with vaccines when data do not suggest a serious risk or signals of serious risk related to the use of the vaccine and when available data to not indicate the potential for serious risk.

[11] Attachment to Letter to Chairman Dingell from Michael O. Leavitt, Secretary HHS, September 27, 2007, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

discuss the design and conduct of the PMRs and PMCs with the review team and provide a timetable for completion of the study or clinical trial for the PMRs and a schedule for milestone submissions and final reports for PMCs.[12] The review team will (1) review the potential study or clinical trial designs to make sure they will serve the purposes of the study and (2) determine whether the proposed timetable will be realistic and provide for timely completion of the study or trial.

Once the wording for the PMRs and to be agreed-upon PMCs has been finalized, the applicant should submit a written agreement to conduct the PMCs. FDAAA gives FDA the authority to require PMRs without prior agreement from the applicant. The PMRs and PMCs will be included in the action letter issued at the completion of the application review.

## V. REPORTING

In general, FDA will interpret the periodic reporting requirement for PMRs and other studies and clinical trials independently conducted (see section 505(o)(3)(E)(ii) in the Act) to be the yearly status reports required under 21 CFR 314.80, 314.81, and 601.70, unless otherwise stated by FDA. Therefore, applicants will be able to report both PMRs and PMCs at the same time and use the format recommended in the guidance on the status of PMCs, as long as the required elements of the PMR information described below are provided in the report. The guidance on the status of PMCs will be updated to reflect FDAAA-related changes.

### A. PMR Reports

For each PMR required under FDAAA, the applicant must submit a timetable for completion of the study or clinical trial and must periodically report on the status of the study or clinical trial (see section 505(o)(3)(E)(ii)). For clinical trials, the report must also include whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trials have been encountered, and registration information as required under section 402(j) of the PHS Act (see section 505(o)(3)(E)(ii)). Registration information for clinical trials should include documentation that the PMR is registered in accordance with Title VIII of FDAAA.[13]

### B. PMC Reports

For each PMC under section 506B of the Act, applicants are required to report annually on the status of the studies or clinical trials (21 U.S.C. 356b(a); 21 CFR 314.81(b)(2)(vii) and

[12] Milestone dates are a series of goal dates (e.g., protocol submission, study or clinical trial start date, final report submission) by which we measure progress of studies and clinical trials and compliance with requirements.

[13] See FDA's guidance *Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007*, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

601.70(b)). The recommendations regarding compliance with section 506B may be found in the guidance on the status of PMCs.[14]

### C. Reports for Studies and Clinical Trials Otherwise Undertaken

For studies or clinical trials independently conducted by an applicant, the applicant must report to FDA under section 505(o)(3)(E)(ii) of the Act and 21 CFR 314.81(b)(2)(viii). These studies or clinical trials are neither required by FDA nor agreed upon between FDA and the applicant.

### D. Reports in REMS Assessments

In addition, section 505-1(g)(3) of the Act at paragraphs (B) and (C) (21 U.S.C. 355-1(g)(3)(B) and (C)) requires that risk evaluation and mitigation strategy (REMS) assessments include the status of postapproval studies and clinical trials required under section 505(o) and those that are otherwise undertaken to investigate a safety issue. Applicants can satisfy these requirements in their REMS assessments by referring to relevant information included in the most recent annual report required under section 506B of the Act and 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in section 505-1(g) could result in enforcement action.

## VI. DISPUTE RESOLUTION

The applicant may appeal a requirement to conduct a postmarketing study or clinical trial using the usual dispute resolution procedures (Guidance for Industry, *Formal Dispute Resolution: Appeals Above the Division Level*)[15] (see section 505(o)(3)(F) of the Act).

## VII. ENFORCEMENT OF REQUIREMENTS FOR POSTMARKETING STUDIES AND CLINICAL TRIALS

The new amendments to the Act give FDA authority to enforce the section 505(o)(3)(E)(ii) requirements for postmarketing studies and clinical trials.[16] An applicant's failure to comply with the timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) will be considered a violation unless the applicant demonstrates good cause for the noncompliance. Under section 505(o)(3)(E)(ii) of the Act, FDA will determine what constitutes good cause.

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[14] See footnote 3.

[15] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[16] FDA has the authority to inspect postmarketing studies and clinical trials, including underlying data and source documents. (See section 505(k) of the Act.)

Enforcement action for a violation of 505(o)(3) could result in one or more of the following:

- Violations of the requirements for postmarketing studies and clinical trials may result in unapproved drug charges. A responsible person[17] may not introduce or deliver into interstate commerce the drug involved if the applicant is in violation of section 505(o) postmarketing study and clinical trial requirements (see section 505(o)(1) of the Act).

- Violations of the requirements for postmarketing studies and clinical trials may result in misbranding charges. A drug is misbranded under section 502(z) of the Act (21 U.S.C. 332(z)) if the applicant for that drug violates postmarketing study or clinical trial requirements, including those outlined in section V above.

- Under section 303(f)(4)(A) of the Act (21 U.S.C. 333(f)(4)(A)), an applicant that violates postmarketing study or clinical trial requirements may be subject to civil monetary penalties of up to $250,000 per violation, but no more than $1 million for all violations adjudicated in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the applicant of the violation. The penalties double for the following 30-day period and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million for all violations adjudicated in a single proceeding. In determining the amount of a civil penalty, FDA will consider the applicant's efforts to correct the violation (see section 303(f)(4)(B) of the Act).

[17] Defined at section 505(o)(2)(A) of the Act.

## GLOSSARY

The following definitions of terms are from section 505-1(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1(b)).

***New safety information*** with respect to a drug, means information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by the Secretary (of Health and Human Services) about —

(A) a serious risk or unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

***Serious adverse drug experience*** is an adverse drug experience that —

(A) results in —

(i) death;

(ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);

(iii) inpatient hospitalization or prolongation of existing hospitalization;

(iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

(v) a congenital anomaly or birth defect; or

(B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

***Serious risk*** means a risk of a serious adverse drug experience.

***Signal of a serious risk*** means information related to a serious adverse drug experience associated with use of a drug and derived from —

(A) a clinical trial;

(B) adverse event reports;

(C) a postapproval study, including a study under section 505(o)(3);

(D) peer-reviewed biomedical literature;

(E) data derived from the postmarket risk identification and analysis system under section 505(k)(4);

(F) other scientific data deemed appropriate by the Secretary.

***Unexpected serious risk*** means a serious adverse drug experience that is not listed in the labeling of a drug, or that may be symptomatically or pathophysiologically related to an adverse drug experience identified in the labeling, but differs because of greater severity, specificity, or prevalence.